



Facile synthesis of Substituted Phenacyl Ethers Using PTC and Crown Ether - A Green Protocol

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ABSTRACT

A Facile and efficient Synthesis of some new substituted Phenacyl ethers (IIa-i) has been carried out with p-methoxy phenacyl bromide and different phenols by using PTC and Dibenzo-[18]-Crown-6. It has been found that, synthesis of substituted phenacyl ethers (IIa-i) using PTC and Crown ether is more effective than by using either PTC or Dibenzo-[18]-Crown-6. The method adopted is operationally simple, Rapid and high yield work up (Green method). The synthesized compounds were analyzed by IR, NMR and Mass Spectroscopic methods.

Keywords: p-methoxy phenacyl bromide, PTC, Dibenzo-[18]-Crown-6, Different phenols.

INTRODUCTION

Aryl ether unit is a common structural unit widely encountered in biologically active molecules and natural products. The linkage C-O-C in ether compounds has significant role in the drug action for e.g. biphenyl ethers and their halo derivatives have agrochemical uses such as herbicides and fungicides¹. Similarly, phenolic ethers find applications in Chemical Engineering², as food coloring materials, perfumes, medicines and additives of polymers³. Some of the ethers are used as synthetic reagents in organic reactions. Ether derivatives are employed as antibiotic such as vancomycin⁴⁻⁸ teicoplanin⁹⁻¹¹ antiviral peptide K-13¹²⁻¹⁴ antitumor, bouvardin¹⁵⁻¹⁶ in pharmaceutical industries.

It has been reported that phenols can be protected as phenacyl ethers which have been synthesized according to traditional method and serve very well for synthetic purpose, as phenacyl ether is more readily cleaved by nucleophiles than other ether. Due to its synthetic utility in organic reaction, we have prompted to undertake a facile synthesis of substituted phenacyl ethers using PTC and Crown ether. Synthesis of phenacyl ethers has been reported by many methods but we have reported the synthesis of phenacyl ethers by adopting Green protocol.

MATERIALS AND METHODS

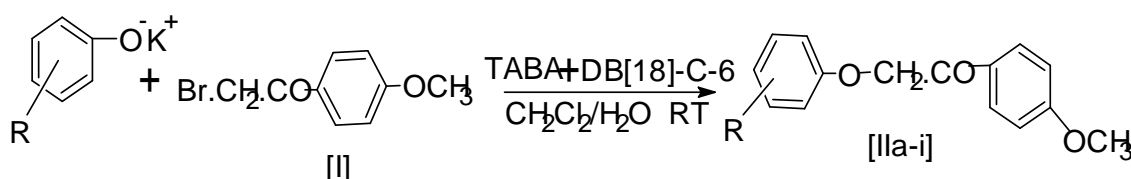
All chemicals were of synthetic grade (S.D. Fine. Chem. Ltd. Mumbai, India). MP were determined by open capillary method and are uncorrected. Products were recrystallized from ethanol as a solvent. The purity of

compound checked by the TLC plate method (Pet ether: Ethyl acetate, 9:1, v/v). The compounds were characterized by using IR, ¹H NMR and Mass spectral analysis. The IR spectra were recorded on Perkin –Elmer spectrum in form of KBr pellet. ¹HNMR was recorded in CDCl₃ on Perkin Elmer R-32 spectrum using TMS as internal standard. Mass spectrums were recorded on El-shimadzu GC-MS spectrometer. The synthesized samples were purified by using Column chromatography (Pet ether and Ethyl acetate system) and recrystallized from ethanol.

p-Methoxy Phenacyl Bromide (Ia-i) were synthesized according to the literature¹⁷.

Synthesis of substituted phenacyl ethers: (IIa-i)

An aqueous solution of compound I (0.05 mmol) prepared by reacting stoichiometric amount of hydroxy aryl compound and aqueous potassium hydroxide containing tetra butyl ammonium bromide (32mg) and dibenzo-[18]-crown- 6(4mg) was added to dichloromethane (2.5ml). The system was stirred for 10 minutes. Then substituted phenacyl bromide II (0.05m mole) was added and the reaction mixture was stirred at room temperature until TLC analysis (Pet ether: Ethyl acetate, 9:1, v/v) indicates completion of reaction. The organic layer was separated and dried over anhydrous sodium sulphate. The solvent was evaporated and the product III was purified by column chromatography. (Pet ether: Ethyl acetate, 9:1, v/v) The products were characterized by NMR, IR, Mass and comparison with authentic samples. SCHEME:



RESULTS AND DISCUSSION

We now reported here an efficient method for synthesis of substituted phenacyl ethers by considering their importance as protecting group and enzyme inhibition. Potassium salt of different phenols on treatment with p-Methoxy phenacyl bromide (I) in two phase system (Water and dichloromethane) in presence of mixture of tetra butyl ammonium bromide and dibenzo-[18]-crown-6 gave corresponding phenacyl ethers (IIa-i) in high yield within a very short time under mild reaction conditions.

We have also carried out etherification of phenol either in presence of tetrabutyl ammonium bromide / dibenzo-[18]-crown-6, But reaction requires more time with low yields. Thus presence of both catalysts plays important role during etherification because here nucleophilicity of the alkoxyanions is enhanced and hence the reaction is completed within very short time (table 1).

Table 1: Effect on synthesis of substituted phenacyl ethers of phenols (0.05 mmol) using different combinations of PTC (TBAB) and dibenzo-[18]-crown-6 at R.T.

Expt.no.	dibenzo-[18]-crown-6(mg)	PTC(TBAB) (mg)	Time (hrs.)	Yield (%)
1	0	32	3.50	88
2	4	0	2.48	89
3	1	32	1.00	90
4	2	32	1.00	91
5	3	32	0.75	92
6	4	32	0.50	95
7	1	48	1.00	91
8	2	48	1.00	91
9	3	48	0.75	93
10	4	48	0.50	95

When reaction was moderated by varying the amount of both catalysts (table 1), mixture of 4 mg of dibenzo-[18]-crown-6 and 32 mg Tetra methyl ammonium bromide was found to be effective in achieving the rapid etherification with high yields (Expt.no.6; table 1).

Table 2: Analytical data of Synthesized compounds (IIa-III):

Compound No.	Phenols	Time [min]	Yield (%)	M.P. (°C)
IIa	Phenol	48	95	83
IIb	α -Naphthol	50	91	58
IIc	β -Naphthol	13	95	110
IId	o-Cresol	28	91	68
IIE	p-Cresol	26	90	61
IIf	o-Nitrophenol	62	88	120
IIg	o-Chlorophenol	19	95	101
IIh	p-Nitrophenol	58	89	154
III	p-Chlorophenol	13	93	89

Table 3: Spectral data of Synthesized compounds (IIa-III):

Com. No.	Phenols	Spectral data
IIa	Phenol	δ , 2.67 (s,3H,-OCH ₃), 5.28 (s,2H,-COCH ₂), 6.72-8.12 (m,9H,Ar-H) ppm. ν_{\max} (KBr): 1695(>C=O), 1215(C-O-C)cm ⁻¹ Mass: m/z [M ⁺] 242.1
IIb	α -Naphthol	δ ,2.59 (s,3H,-OCH ₃), 5.4(s,2H,-COCH ₂), 7.4-8.15 (m,12H,Ar-H) ppm. ν_{\max} (KBr):1695(>C=O),1215(C-O-C) cm ⁻¹ Mass: m/z [M ⁺] 292.3
IIc	β -Naphthol	δ ,2.57 (s,3H,-OCH ₃),5.49 (s,2H,-COCH ₂), 7.4-8.15 (m,12H,Ar-H) ppm. ν_{\max} (KBr):1695(>C=O),1215(C-O-C)cm ⁻¹ Mass: m/z [M ⁺] 292.1
IId	o-Cresol	δ ,2.19 (s,3H,-CH ₃),2.62 (s,3H,-OCH ₃), 5.2 (s,2H,-COCH ₂) 6.72-8.12 (m,9H,Ar-H) ppm. ν_{\max} (KBr):1695(>C=O),1215(C-O-C)cm ⁻¹ Mass: m/z [M ⁺] 256.4
IIE	p-Cresol	δ ,2.24 (s,3H,Ar-CH ₃), 2.65(s,3H,-OCH ₃), 5.2 (s,2H,-COCH ₂), 6.72-8.12 (m,9H,Ar-H) ppm. ν_{\max} (KBr):1695(>C=O),1215(C-O-C)cm ⁻¹ Mass: m/z [M ⁺] 255.9]
IIf	o-Nitrophenol	δ ,2.59 (s,3H,-OCH ₃),5.43 (s,2H,-COCH ₂), 6.78-7.6 (m, 7H,Ar-H) ppm. ν_{\max} (KBr):1695(>C=O),1215(C-O-C)cm ⁻¹ Mass: m/z [M ⁺] 287.1
IIg	o-Chlorophenol	δ ,2.60 (s,3H,-OCH ₃), 5.21 (s,2H,-COCH ₂), 6.78-7.6 (m, 7H, Ar-H), 7.8 (d,2H,ortho to -COCH ₂) ppm. ν_{\max} (KBr):1695(>C=O),1215(C-O-C)cm ⁻¹ Mass: m/z [M ⁺] 276.5 ;[M ⁺ +2] 278.5
IIh	p-Nitrophenol	δ ,2.66 (s,3H,-OCH ₃), 5.39 (s,2H,-COCH ₂) 6.78-7.6 (m, 7H,Ar-H) ppm. ν_{\max} (KBr):1695(>C=O),1215(C-O-C)cm ⁻¹ Mass: m/z [M ⁺] 286.8
III	p-Chlorophenol	δ ,2.67 (s,3H,-OCH ₃), 5.24 (s,2H,-COCH ₂) 6.76-8.12 (m,9H,Ar-H) ppm. ν_{\max} (KBr):1695(>C=O),1215(C-O-C)cm ⁻¹ Mass: m/z [M ⁺] 276.5; [M ⁺ +2] 278.5

CONCLUSION

We have synthesized different substituted p-methoxy phenacyl ethers by using green protocol. It has been found that, the rate of reaction takes place slow with phenols containing electron withdrawing substituent's, while it takes fast for phenols containing electron donating substituent's. The time required for etherification by using polar solvent is less than that of non polar solvent. The merits of current protocols are:

1. Reaction carried out at Room Temperature.
2. Use of solid supported green reagents i.e. PTC and Crown ether.

3. Yields are excellent.
4. It requires short reaction time.
5. Multistep synthesis is avoided (single step).

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